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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,766	07/06/2001	Goran Forsberg	P02188US0 (10104199)	7699

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)	
09/900,766	Forsberg et	
Examiner	Group Art Unit	
Duffy	1645	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 9-9-03.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 15, 22-34, 53, 60-72 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 15, 22-34, 53 + 60-70. is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). 14

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Pat nt Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

DETAILED ACTION

1. The response filed 9/9/2003 has been entered into the record. Claims 15, 22-34, 53 and 60-72 are pending, claims 1-14, 16-21, 54-59 and 73-92 having been canceled.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

3. The objection to the disclosure is withdrawn in veiw of Applicants' amendments.

Information Disclosure Statement

4. The information disclosure statement filed 9-9-03 has been considered. An initialed copy is enclosed.

Rejections Withdrawn

5. The 112, second paragraph rejections in regard to "low titer" and relative positions in a sequence in the absence of a sequence identifier are withdrawn in view of Applicants' amendments.

The art rejection under 35 U.S.C. 102(b) is withdrawn based on Applicants amendments.

Rejections Maintained

Claim Rejections - 35 U.S.C. § 112

6. Claims 15, 22-34, 53 and 60-72 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons made of record in Paper No. 11, mailed 5-9-03.

Applicants' arguments have been carefully considered but are not persuasive. Applicant argues that regions A-E of the present inventions that contain antibody binding sites, as shown in figures 1, 2, 4 and Figure 4 shows the sequence alignment of SEA, SEE, SEA/E-18 and SEA/E-120 along with regions A-E which are defined as the lines above the sequences. Moreover, it is well established that antibody binding to epitopes can be influenced by changes to the amino acid sequence outside of the eptiope region. Additionally, the art of record names at least regions A, B, C, D, E, F, G and H (see WO 97/36932 page 5, lines 26-35). As such, recitation of "Regions A-E" does not discretely define any portion of SEE to a person of skill in the art. Further, Applicants' arguments

make no sense in regard to the description of Figure 4, because region A is apparently defined (by the underlining) therein as 9 amino acids and region C as 11 amino acids and therefore it is inconceivable as to how to substitute 15 residues in region C, when region C is only 11 amino acids in length. Therefore, this argument is not persuasive, limitations of the specification are not read into the claims and the claims do not recite the regions comprise seroreactive epitopes and the language of the claims specifically conflicts with Applicants' asserted regions. Applicants also argue that one of skill in the art would be ale to make substitution in any of the various regions using molecular biology techniques and Table 1, Figure 7, 8A and 8B provide examples of chimeric molecules having mutation in the identified regions or which show reduced seroreactivity. This is not persuasive, the seroreactivity comparison is restricted to that evidenced by SEA/E-18 and not the native or any mutant "derived from". Additionally, Table 1, makes it clear that random substitutions have a unpredictable outcome on the ability to retain SADCC. Reduction in seroreactivity as compared to SEA/E-18 leads to unpredictable results regarding this critical feature of a superantigen. For example multiple mutants comprising the identical C-region mutations have different biological properties, including seroreactivity, SADCC and SDCC. Further, Table 1 does not provide any information in regard to seroreactivity of individual mutants of claimed region A as it relates to seroreactivity it is derived from. The base starting point for variation was SEA/E-18 and not the native sequence of SEE and SEA/E-18 has substitutions

at positions 20, 21, 24 and 27. As such, the specification is devoid of description of the effect, if any of positions 20, 21, 24 and 27 with regard to reduced seroreactivity compared to the superantigen from which it is derived. Applicants argue that the specification teaches how to use the cytokine as an adjuvant aor make fusion proteins comprising a tri-partite conjugate and PCT WO99/04820 teaches how to make a tripartite conjugate as well as the benefit of a conjugate for reducing the amount of tumors. This is not persuasive. As set forth by the examiner, the tripartite fusion exhibits substantially reduced affinity and PCT WO99/04820, unlike the instant specification provides specific information regarding the biological activity of a specific tripartite conjugate in vivo to a specific melanoma antigen. In the instant case, no data regarding treatment of lung tumors or cancer of the lung has been provided by the specification. Applicants argue that they need not repeat what is will known in the art and cites the corresponding case law. This is not persuasive, treatment of lung cancer is with SADCC is not well known or even established in the art at the time that this invention was made. PCT WO99/04820 specifically acknowledges that the binding affinity of the tripartite conjugate is significantly lower (paragraph bridging page 42) and moreover involves a different superantigen. Different superantigens as demonstrated the art of record have different biological properties. Table 1, clearly indicates that the claimed mutants have reduced seroreactivity, and Table 1 indicates that reduction of seroreactivity unpredictably effects SADCC. If you can not kill a cell by

SADCC, then the addition of IL-2 would not appear to enhance any effect and in a tripartite conjugate may sterically hinder binding and activity of the superantigen. Additionally, PCT WO99/04820 provides for a specific orientation of the members of the tripartite conjugate, a orientation that is not reflected in the instant claims and is limited to a modified IL-2. Applicants argue that SEA/E-18 retained an efficient level of cytotoxicity as SEA as recited in paragraph [160] of the specification. This is not persuasive, the claims merely require reduced seroreactivity as compared to what they are "derived from". The specification acknowledges that SEE has markedly decreased cell killing properties with fused to a specific tumor Fab. Applicants arguments regarding the mutant SEA/E-18 are clearly not commensurate in scope with the claims. The specification provides no information regarding the biological effects of the claimed individual mutations, only specific mutations in combination with one another in relation to SEA and not SEE from which it is derived from. Table 1, merely emphasizes that mutating other portions may reduce seroreactivity as compared to the SEA/E-18, does not predictably effect SADCC. SADCC is critical to in vitro killing and Table 1, clearly demonstrates that mutations unpredictably effect this biological activity and demonstrates that mere reduction in seroreactivity does not predictably correlate with cell killing. Applicants argue that the biological activity of inducing cell death in vitro correlates with in vivo cell death. This is not persuasive, the biological property in the claim is a reduction of seroreactivity, not

induction of SADCC. Furthermore, it is clear from Table 1 that reduction of seroreactivity does not predictably correlate with the biological activity of SADCC as such, Applicants are arguing limitations that are not present in the claims. Applicants also argue Forsberg et al supports the relevance of 5T4 and the conjugate 5T4FabV13-SEAD227 in non-small cell lung cancer therapy. This is not persuasive, because it does not address the superantigens as claimed and also the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

For the foregoing reasons, the rejection is maintained.

7. Claims 15, 22-34, 53 and 60-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With respect to claims 15, 16, 18-34, 53, 54 and 56-72, the claims are prima facie indefinite from the use of the terminology "Region C", "Region A" and "Region E" because neither the specification or claims define these particular regions on any enterotoxin is maintained for reasons made of record. Applicants argue that these regions are defined in Figure 4. This is not persuasive. Figure 4 indicates that region A has 9 amino acids, region B has 16 amino acids, region C has 11 amino acids, region D has 4 amino acids and region E has 11 amino acids. As such, the claims are still confusing because the claims recite

substitutions of "..so that nor more than 15 amino acid residues in region C are replaced with different amino acids.." and so on. This is inconsistent with Applicants asserted defined regions in Figure 4. The metes and bounds of the claimed regions have not been clearly set forth in the specification and is in conflict with the claims such that one skilled in the art would be able to ascertain that which is included or excluded by this claim language. Additionally, limitations from the specification are not read into the claims. As such, the claims remain indefinite.

Status of Claims

8. No claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 9:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308-3909.

Patricia A. Duffy, Ph.D.
December 1, 2003

Patricia A. Duffy, Ph.D.
Primary Examiner
Group 1600